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A. Denys, E. Guilbert-Ber, and Jeanne Levy

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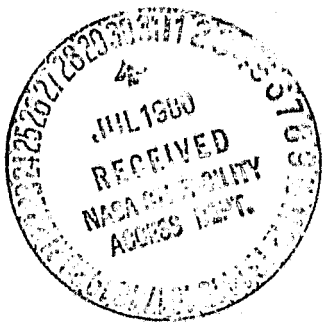

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16. Abstract

Restraint or exposure to a cold environment (0°) for three hours mobilizes the chlordane stored in the adipose tissue of mice pre-treated with this inductor.

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CHARACTERISTICS OF ENZYMATIC INDUCTION PROVOKED BY CHLORDANE

A. Denys, E. Guilbert-Ber and Jeanne Levy*

IV. Influence of different procedures induced in mice by chlordane**

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In a previous publication (1973), we established that, in mice pretreated with chlordane, electroshock is capable of increasing the degree of previously acquired induction. The results of experiments performed with an inhibitor of protein synthesis, allows us to show that electroshock is capable of mobilizing the chlordane stored in the adipose tissues of mice.

In the present work we are examining the effects of other varieties of stresses such as restraint, lowering or elevation of the environmental temperature, in mice pretreated with chlordane in conditions analogous to those in which electroshock raises the degree of previously acquired induction.

Techniques

Experimental Animals. We use pubescent male Swiss mice, with age varying from 5 to 19 weeks, kept in groups of 10.

Inductor. We employed so-called "technical" commer- /278 cial chlordane in corn oil solution at a concentration of

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0.25 to 0.75% according to the dose (2.5 to 7.5 mg/kg) and administered by the intraperitoneal route (i.p.) 0.2 ml per 20 gm of mouse.

Two types of treatment were given:

a) single dose: 7.5 mg/kg i.p.;

b) the type of treatment established in our previous experiments (2.5 mg/kg i.p. injected daily for three consecutive days).

Stresses

1° Restraint. Restraint is accomplished by forced immobilization of a mouse introduced into an altuglass cylinder, of a length and diameter varying according to the size of the mice. The cylinder is perforated with three rows of aeration holes, the perforated stopper allows the animal's tail to pass through; this as well as the cylinder itself are immobilized by means of adhesive tape on a fixed horizontal plane.

All the mice are experimented upon 24 or 48 hours after the restraint.

2° Serial exposure to different ambient temperatures. The mice, kept in lots of 10 in their usual cage, are placed for three hours either in a cold chamber at 0 $\pm$ 0.5° C, or in an enclosure regulated at 10 $\pm$ 1.32 $\pm$ 1, and 38 $\pm$ 1°C.

All the mice are experimented upon 24 or 48 hours after the stress.

Effectors. - Pentobarbital is administered in an 0.5% solution at a dose of 100 mg/kg i.p.

Zoxazolamine is administered, after solution by N HCl, in a 1% solution, at a dose of 100 mg/kg i.p.

The duration of the sleep induced by the pentobarbital, or of the paralysis induced by the zoxazolamine, corresponds to the period of time occurring between the disappearance of the posture reflex and the recovery of the mouse placed, after the latent period, on his back and maintained at a temperature of 21 $\pm$ 1°C.

All the experiments were performed in a comparative manner on groups of 20 induced mice whether subjected or not to the stress and on controls of the same age.

The average durations of sleep or paralysis were established by considering all the experimental mice, whether they slept or not, and whether they were paralyzed or not.

The results are expressed as in our previous articles: M or M_1 (for inducted mice whether subjected to the stress or not), M' or M'_1 (for controls whether submitted to the stress or not).

The coefficient P is defined by the formula $\frac{M}{\overline{M}'} \times 100$, which implies that before any induction P = 100.

Inhibition of Protein Synthesis. Ethionine is administered in a 2% solution at a dose of 200 mg/kg i.p. 30 minutes before the stress.

RESULTS /279

Study of the effects of the diverse stresses, restraint, lowering or elevation of the environmental temperature, imposed

on mice whether pretreated with chlordane or not, furnished the results reported below.

Restraint

1. Induction by Chlordane followed by restraint.

The experiment is conducted, either on five to ten week old mice, or else on eighteen week old mice. One to five days after the induction by chlordane (treatment type or massive dose), the mice are subjected to a three hour long immobilization, followed by rest periods (24 or 48 hours) before the administration of the effector pentobarbital. The durations of sleep of the control mice, whether induced by chlordane or not (M and M') are compared to those of the mice inducted or not by chlordane and subjected to the restraint (M_1 and M'_1).

1° The results, given in table I, can be summarized as follows: before the administration of the effector, present the same reactivity as that of the controls not subjected to restraint: M'_1 is not significantly different from M'.

2° Whatever the age of the mice, who were pretreated with chlordane (treatment type), five to eighteen weeks old, restraint imposed for 24 or 48 hours before administration of the pentobarbital, provokes a greater significant decrease of the duration of sleep than that observed in inducted mice not subjected to this stress.

In contrast, pretreatment with a single dose of chlordane (7.5 mg/kg) is not associated with the same phenomenon; restraint imposed 48 hours before the administration of the pentobarbital does not significantly change the duration of sleep of the inducted mice.

3° The effects of restraint on the duration of sleep of inducted mice decreases with time. In our experiments, they are no longer perceived four to twelve days after the immobilization of the mice.

Intensity of the influence of restraint on the induction provoked by chlordane

Table I: INFLUENCE OF RESTRAINT ON THE INDUCTION PROVOKED BY CHLORDANE

Treatment type	Time (days)	Chlordane (mg/kg)	without restraint: Controls M' (min.)	without restraint: Inducted M (Min.)	p	With restraint: Controls M'1 (min)	With restraint: Inducted M1 (min.)	p
			5 to 10 wk. old mice					
	1	2.5						
	2	2.5	the 4th day.					
	3	2.5						
	5		44 ± 3.7	17 ± 1.6	39 ***	56 ± 9.5	8 ± 2.9	18 °°
	1	2.5						
	2	2.5						
	3	2.5						
	5		52 ± 3	18 ± 2.6	35 ***	43 ± 3.4	8 ± 1	15 °°°
	9		34 ± 2	17 ± 2.9	50 ***	30 ± 3.2	8 ± 0.9	24 °°
	11		34 ± 2.5	15 ± 1.7	44 ***		10 ± 1.4	29 °
	16		30 ± 1.7	16 ± 1.7	53 ***		12 ± 1.7	40
			Restraint the 8th day					
	1	2.5						
	2	2.5						
	3	2.5						
	10		24 ± 1.7	12 ± 1.8	50 ***	20 ± 2.2	7 ± 1.1	29 °
	12		27 ± 2.5	14 ± 1.7	52 ***		8 ± 1.4	30 °°
			11- 18 week old mice. Restraint the 8th day					
	1	2.5						
	2	2.5						
	3	2.5						
	10		56 ± 4.9	26 ± 2.4	46 ***	52 ± 3.2	18 ± 2	32 °°
			-10 week old mice. Restraint the 6th day					
Single dose	1	7.5						
	8		35 ± 2.7	20 ± 1.4	57 ***	37 ± 3	17 ± 1.3	49

*** : $p < 0.001$ in comparison to the controls
° : $p < 0.05$; °° : $p < 0.01$; °°° : $p < 0.001$ in comparison to inducted but unrestrained mice.

We have established that a booster dose of chlordane of 2.5 mg/kg, administered to mice previously inducted by the treatment type, 48 hours before the pentobarbital, exerts an action comparable in intensity to that of the restraint. The duration

of sleep of the mice having received the booster dose is not different from that of mice subjected the same day to a three hour restraint. The results of the experiment are contained in table II.

Action of ethionine on the effects of restraint imposed on mice inducted by chlordane

Ethionine is administered 30 minutes before the restraint at a dose of 200 mg/kg i.p; pentobarbital is injected before the restraint, either 24 hours and 7 days for series 1, or 2 and 4 days for series 2, or 2 days for series 3.

TABLE II. COMPARISON OF THE EFFECTS OF RESTRAINT TO THOSE OF A BOOSTER DOSE OF CHLORDANE IN MICE PREVIOUSLY INDUCTED BY THE TREATMENT TYPE. EFFECTOR: PENTOBARBITAL (50 mg/kg i.p.)

	1st series Mice 8 to 9 weeks old Duration of sleep (mn)	p	2nd series 18 week old mice Duration of sleep (mn)	p
controls	27 ± 2,5		56 ± 4,9	
inducted mice	14 ± 1,7	52***	26 ± 2,4	46***
inducted mice & restraint	8 ± 1,4	30**	18 ± 2	32**
Inducted mice + chlordane booster	7 ± 1,4	26**	19 ± 1,8	34**

** : $p < 0.05$; ** : $p < 0.01$ in comparison to inducted mice
*** : $p < 0.001$ in comparison to non-inducted controls

The results contained in Table III permit the following observations:

1. Pentobarbital provokes identical effects in non-inducted controls subjected or not to restraint, either in the presence or the absence of ethionine.

2. Ethionine, administered to mice previously inducted by chlordane (treatment type) 30 min. before restraint, combats the effects of the latter drug; the duration of sleep tends to equal that of the inducted but non-restrained mice without, however,

TABLE III. INFLUENCE OF ETHIONINE ON THE EFFECTS OF RESTRAINT IMPOSED ON MICE BY CHLORDANE (TREATMENT TYPE)
EFFECTOR: PENTOBARBITAL (50 mg/kg i.p.)

	Time (days)		Without ethionine Duration of sleep	P	With ethionine Duration of sleep (min.)	P
		7 to 9 week old mice restraint the 4th day				
Series 1	5	Controls	27 ± 1.7			
	5	Controls + restraint	29 ± 2.2	107	28 ± 1.9	104
	5	Inducted mice	11 ± 1.3	41***		
	5	Inducted mice & restraint	5 ± 1.3	19***	16 ± 1.5	59***
	11	Témoins	24 ± 2.2			
	11	Induites	8 ± 1.3	33***		
	11	Induites + contrainte	3 ± 0.9	13***	3 ± 0.9	13
		Restraint the 8th day.				
Series 2	10	Controls	24 ± 1.7			
	10	Controls +Restraint	20 ± 2.2	83	30 ± 2.4	125
	10	Controls	12 ± 1.8	50***		
	10	Controls+Restraint	7 ± 1.1	29°	14 ± 2.2	58••
	12	Controls	27 ± 2.5			
	12	Inducted	14 ± 1.7	52***		
	12	Inducted +Restraint	8 ± 1.4	30°°	10 ± 1.4	37
Series 3		Controls+Restraint estraint or booster the 8th day				
	10	Controls	56 ± 4.9			
	10	Controls	52 ± 3.2	93	61 ± 4.5	109
	10	Inducted	26 ± 2.4	46***		
	10	Inducted+Restraint	18 ± 2	32°°	32 ± 2.7	57•••
	10	Inducted and booster	19 ± 1.8	34°	28 ± 3.5	50•

***: $p \leq 0{,}001$ in comparison to non-inducted controls
°: $p \leq 0{,}05$; °°: $p \leq 0{,}01$; °°°: $p \leq 0{,}001$ in comparison to inducted mice
•: $p \leq 0{,}05$; ••: $p \leq 0{,}01$; •••: $p \leq 0{,}001$ in comparison to inducted mice subjected to restraint or to chlordane booster.

reaching the duration of sleep of the non-inducted controls.

And so for series 1 and 2, ethionine re-establishes the duration of sleep respectively to 16 ± 1.5 instead of 5 ± 1.3 min. and to 14 ± 2.2 instead of 7 ± 1.1. min.

3. The effects of the ethionine are fleeting. They have disappeared already at four days after administration, in such a manner that the durations of sleep of the inducted mice subjected to restraint, either in the absence or presence of ethionine, are equal (2nd series).

4. The influence of ethionine, administered 30 min. before the injection of a chlordane booster (2.5 mg/kg) is comparable to that which this inhibitor of protein synthesis exerts in regard to restraint (3rd series); this increases the duration of sleep in two cases, 28 ± 3.5 instead of 19 ± 1.8 min. (booster injection), and 32 ± 2.7 instead of 18 ± 2 min. (restraint).

II. RESTRAINT PRECEDING THE INDUCTION

Restraint imposed before induction with a single dose of chlordane on lots of 40 mice, does not change the duration of sleep provoked by pentobarbital (Table IV)

TABLE IV. INFLUENCE OF RESTRAINT PRECEDING INDUCTION BY A SINGLE DOSE OF CHLORDANE. 5 to 9 WEEK OLD MICE.

Effector: pentobarbital (50 mg/kg i.p.).

Chlordane (mg/kg)	without restraint duration of sleep (min.)	p	with restraint Duration of sleep (min.)	p
0	34 ± 1.7		30 ± 1.7	88
5	17 ± 0.8	50	17 ± 1.6	50
7.5	10 ± 0.7	29 ***	12 ± 1.1	35

*** : p ≤ 0.001 Between mice inducted by 5 and by 7.5 mg/kg of chlordane.

STRESS CONSISTING OF AN ABRUPT LOWERING OF THE ENVIRONMENTAL TEMPERATURE

I. INDUCTION BY CHLORDANE FOLLOWED BY THE STRESS

In preliminary experiments, we progressively lowered the environmental temperature.

We did not observe any significant change of the duration of sleep in the controls or in the inducted mice, exposed for 3 hours, 5 hours and 24 hours to a temperature of 10 $\pm$ 1°. /283

In contrast, a stay of three hours at 0 $\pm$ 0.5° leads to significant results.

The experiment is conducted on five to ten week old mice. The exposure to 0° for three hours took place at 24 hours or five days after the administration of the last dose of chlordane (treatment type). Pentobarbital or zoxazolamine are injected at varying times after the stress, but always at least 24 hours after it.

The results which appear in table V, can be summarized as follows:

1. The non-inducted mice, exposed for three hours at 0°, 24 or 48 hours before the administration of the effector, present the same reactivity as the controls not subjected to the stress: M'_1 is not significantly different from M'.

2. The inducted mice, exposed for three hours at 0°, have a decreased duration of sleep or paralysis compared to that of the inducted mice not subjected to the cold: M_1 is significantly different from M.

3. The effects of the stress by cold diminish progressively with time. In our experiments, they were still weakly significant ($p \leq 0.05$) 15 days after the stress.

TABLE V. INFLUENCE OF EXPOSURE TO COLD (3 HOURS AT 0°C) ON THE INDUCTION PROVOKED BY CHLORDANE (TREATMENT TYPE).

7 to 9 week old mice

Effectors: pentobarbital (50 mg/kg i.p.) and zoxazolamine (100 mg/kg ip)

Time (days)	Chlordane (mg/kg)	Without stress: Non-inducted M' (mm)		Inducted M (min.)		P	With stress: Non-inducted M' (min.)		Inducted M_1 (min.)		P
1st series: Pentobarbital. Exposure to 0°C the 4th day.											
1	2.5										
2	2.5										
3	2.5										
5		37	2.2	17	1.6	46 ***	38	3	10	1.1	27 ***
8		40	3.2	17	2.4	43 ***			14	2	35
2nd series: Pentobarbital. Exposure to 0°C the 8th day.											
1	2.5										
2	2.5										
3	2.5										
10		44	3	16	1.6	36 ***	48	4	12	1.2	27 *
12		47	2.7	21	2.3	45 ***			11	1.1	23 ***
16		49	1.3	27	3.5	55 ***	45	5.7	17	1.3	35 **
23		53	2.6	31	3.4	58 ***			22	1.5	42 *
3rd series: Zoxazolamine. Exposure to 0° the 8th day.											
1	2.5										
2	2.5										
3	2.5										
10		23	2.6	7	0.8	30 ***	21	2	4	0.5	17 **

*** $p < 0.001$ in comparison to the non-inducted controls

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$ in comparison to the inducted mice.

Let us note that the body temperature of the mice, immediately after the three hour stay at 0°, was unchanged (38.9° as opposed to 38.6° at time 0).

These results do not disagree with those of ESTLER, AMMON and LANG (1970) who showed that 78% of mice maintained 4 hours at 0° are capable of maintaining their previous body temperature.

Intensity of the influence of a 3 hour stay at 0° on the induction provoked by chlordane.

We established that a booster dose of chlordane (2.5 mg/kg) administered to inducted mice (treatment type), on the 8th day of the experiment and four days before the pentobarbital, exerts an effect comparable in intensity to that of the exposure to cold (the stress and the administration of the booster dose following the same chronology).

[illegible] of ethionine on the effects of the stress by cold in mice inducted by chlordane

Ethionine is administered 30 min. before the exposure to cold; pentobarbital is injected two and four days after the stress (table VII).

The results make possible the following conclusions:

1. Ethionine does not modify the duration of sleep of the non-inducted controls.

TABLE VI. COMPARISON OF THE EFFECTS OF EXPOSURE TO COLD (3 hr. AT 0° TO THOSE OF A BOOSTER DOSE OF CHLORDANE (2.5 mg/kg) IN MICE PREVIOUSLY INDUCTED BY THE TREATMENT TYPE. 7 to 9 WEEK OLD MICE.

EFFECTOR: PENTOBARBITAL (50 mg/kg i.p.)*

	Duration of sleep (mn)	p
Controls	47 ± 2.7	
Inducted	21 ± 2.3	45 ***
Inducted + booster of chlordane	11 ± 1	23 °°°
Inducted + exposure to cold	11 ± 1.1	23 °°°

*: administered 4 days after the booster dose or the exposure to cold

***: $p < 0.001$ in comparison to the controls

°°°: $p < 0.001$ in comparison to the inducted mice.

2. Ethionine combats the effects of aggression as well as those of a booster dose of chlordane in mice previously inducted by either of them.

3. Ethionine exerts only a fleeting action which disappears in 48 hours.

II. EXPOSURE TO COLD PRECEDING THE INDUCTION /286

Exposure to 0°, for three hours preceding by 24 hours the induction by a single dose of chlordane, does not change the duration of sleep provoked by pentobarbital (table VIII).

STRESS CONSISTING OF AN ABRUPT ELEVATION OF THE ENVIRONMENTAL TEMPERATURE

TABLE VII. INFLUENCE OF ETHIONINE ON THE EFFECTS OF EXPOSURE TO COLD (3 HR. AT 0°C) IN MICE INDUCTED BY CHLORDANE (TREATMENT TYPE) 7 to 9 WEEK OLD MICE. EFFECTOR: PENTOBARBITAL (50 mg/kg i.p.)

Time (days)		Without ethionine duration of sleep (min.)	P	With ethionine* Duration of sleep	P
10	controls	44 ± 3		46 ± 2.4	104
10	Inducted	16 ± 1.6	36***		
10	Inducted + exposure to cold the 8th day	12 ± 1.2	27"	19 ± 2	43••
10	Inducted + chlordane booster the 8th day	10 ± 0.9	23""	17 ± 1.5	39•••
12	Controls	47 ± 2.7			
12	Inducted	21 ± 2.3	45***		
12	Inducted + exposure to cold the 8th day	11 ± 1.1	23""	12 ± 0.8	26
12	Inducted + chlordane booster the 8th day	11 ± 1	23""	10 ± 1.3	21

(*) 200 mg/kg before the exposure to cold or the booster dose of chlordane

***: $p \leq 0.001$ in comparison to the controls

": $p \leq 0.05$; "": $p \leq 0.01$; """: $p \leq 0.001$ in comparison to the inducted mice

••: $p \leq 0.01$; •••: $p \leq 0.001$ in comparison to the inducted mice having undergone either the stress or the booster dose

TABLE VIII. INFLUENCE OF EXPOSURE TO COLD (3 hr. at 0°C) PRECEDING BY 24 HOURS THE INDUCTION BY A SINGLE DOSE OF CHLORDANE 7 to 9 WEEK OLD MICE

EFFECTOR: PENTOBARBITAL (50 mg/kg)

Chlordane (mg/kg)	Controls Duration of sleep (min).		Mice exposed to 0°C Duration of sleep (min).	p
0	31 ± 1.5		28 ± 2.8	90
2.5	20 ± 1	65	19 ± 0.9	61
5	16 ± 0.8	52**	18 ± 1.2	58

* administered 48 hr. after the chlordane

**: $p < 0.01$ between the mice inducted by 2.5 and by 5 mg/kg of chlordane.

TABLE IX. INFLUENCE OF EXPOSURE TO 32+1°C ON INDUCTION PROVOKED by CHLORDANE (TREATMENT TYPE). 5 to 10 WEEK OLD MICE

EFFECTOR: PENTOBARBITAL (50 mg/kg i.p.)

Time (days)	Chlordane mg/kg	Without stress Non-induced M'_1 (min.)	Inducted (min)	p	With stress Inducted M_1 (min)	Non-induced M'_1 (min)	
		Exposure to 32° the 8th day					
1 2 3	2.5 2.5 2.5						
10		48 ± 3.1	15 ± 1.25	31***	51 ± 5.3	17 ± 1.7	35

***: $p < 0.001$ In comparison to the non-inducted controls.

The experiment is carried out on lots of 20 five to ten week old mice, chronically inducted by chlordane (treatment type); five days after the last dose of the inductor, the inducted mice and the controls are placed for three hours in an enclosure maintained either at 32°C ± 1, or at 38°C ± 1. Pentobarbital is administered two days after the stress.

The stay at 32°C (close to thermal neutrality) caused no /287 change in the rectal temperature of the controls (37.8 ± 0.07°C). The same observations were made by DOSS and OHNESORGE (1966) who exposed mice for two and a half hours either at 20°C or at 30°C

and observed temperatures respectively of 36.6 ± 0.05 and of 36.8 ± 0.06°C.

The results concerning the inducted mice and the controls, shown in table IX, show that exposure to 32°C for three hours did not influence the induction of the previously established mice.

As for the stay at 38°C, it caused for both the controls and the inducted mice, first, an elevation of the rectal temperature (40.2° instead of 37.6°C) and lastly, a mortality which varied for the different experiments from 15 to 44%.

DISCUSSION

In the present work. we subjected mice previously inducted with chlordane to three types of stress: restraint, lowering and elevation of the environmental temperature for a three hour duration.

We have shown that restraint and abrupt lowering of the environmental temperature to 0° increase the effects of previously acquired induction.

In contrast, in mice maintained at 32 ± 1°C, a temperature near to thermal neutrality, no phenomenon of supplementary induction is observed (table IX). As for mice, inducted and control, exposed to 38 ± 1°C, they undergo a body temperature elevation engendering a mortality too great to permit worthwhile conclusions.

It turns out from all of our experiments that electroshock (DENYS, GUILBERT-BER and LEVY, 1973), restraint and lowering of the environmental temperature increase the effects of the induction acquired by a previous treatment with chlordane, in regard to the effectors used.

We concluded from our experiments that the increase of the intensity of previously acquired induction under the influence of electroshock, results from a mobilization of the chlordane stored in the adipose tissues.

Do the same conclusions thrust themselves forward for the two new stresses studied above?

To this end, after having established an accrued decrease (tables I and III) of action of the effectors (pentobarbital for restraint and pentobarbital plus zoxazolamine for lowering of the ambient temperature), we have:

1. determined the booster dose of chlordane (2.5 mg/kg administered to mice previously inducted by the treatment type), which provokes a supplementary induction with an intensity of the same order of magnitude as that provoked by one or the other of the stresses being studied (tables II and VI);

2. demonstrated that the supplementary induction provoked by either of the stresses (tables III and VII) is suppressed by ethionine;

3. verified that the stresses preceding induction do not change it (tables IV and VIII). /288

These results, parallel to those obtained in the experiments dealing with electroshock, show that restraint and a limited stay in an environment maintained at 0°, provoke an induction supplement adding on to that previously acquired.

This "re-induction" can be attributed to a discharge of chlordane stored in the adipose tissue, since the stresses do not act directly on the hepatic enzyme systems which metabolize the effectors employed.

We intend to examine further, on the one hand, to what degree chlordane mobilization under the influence of certain types of stresses is observable in the rat, and on the other, the possible relationships between chlordane mobilization and the phenomenon of lipolysis.

CONCLUSIONS

1. We submit that two types of stresses, restraint or a stay in an environment maintained at 0° for a three hour duration, increase the degree of induction previously acquired in mice pre-treated with chlordane; their effects are comparable to the effects engendered by a booster dose of chlordane and, as with it, are combatted by ethionine.

2. These two stresses are, like electroshock, capable of mobilizing the chlordane stored in the adipose tissue of the mouse.

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